Remarks

Claims 45-86 are pending. Claims 45, 55, 60, 61, 67, 68, 79, 80 and 86 have been amended.

Claim Rejections under 35 USC 112

In response to the rejection of the claims as failing to comply with the written description requirement, and for indefiniteness, Applicants have herewith amended the claims to cancel reference to the term "prodrug." Thus, this rejection has been overcome and the Examiner is requested to remove the stated rejection.

With respect to the assertion that claim 47 is a duplicate of claim 46, and in respect of the same rejection imposed upon claims 59 and 55, 66 and 64, 78 and 78, and 86 and 82, respectively, Applicants disagree that claim 47 is duplicative of claim 46, as claim 46 recites a composition comprising ambroxol or its salts and at least one inhibitor of the angiotension-converting enzyme. Applicants are unclear as to how claim 46 could be construed as directed only to a "compound," given that it includes at least two distinct members. Further, claim 46 is directed to a composition which could, for example, be utilized in vitro and therefore not necessarily comprise pharmaceutical carriers, additives and/or adjuvants. The same rationale applies to the other cited composition claims. With respect to the method claims that have been deemed duplicative, Applicants disagree because a composition delivered to an individual in a method of treatment does not necessarily require additives and/or adjuvants, as those claims recite. The Examiner is thus requested to remove the stated rejections.

In response to the rejection based upon lack of enablement for treating the recited diseases, Applicants point out that the specification provides working examples demonstrating that a combination of α-lipoic acid, ambroxol and an inhibitor of angiotensin-converting enzyme (ACE) promotes survival of neuronal cells after oxygen glucose deprivation (OGD) (see Examples 2 and 3). In connection with this, Applicants enclose herewith a declaration under 37 CFR 1.132 from Dr. Frank Striggow, an inventor on the present application and a recognized expert in the field of neurodegenerative diseases. Dr. Striggow's declaration provides supporting information illustrating unexpected properties of co-administration of ambroxol and an ACE inhibitor, such as

enalapril. Moreover, the declaration highlights that the effect of co-administration of these compounds is synergistic; namely, it is greater than the sum of the effects achieved by the sole administration of ambroxol or sole administration of an ACE inhibitor.

In particular, the data in Figure 1 appended to the Declaration demonstrate the effectiveness of the invention in a clinically relevant **in vivo** global ischemia gerbil model. As noted in Dr. Striggow's Declaration, the data used to create this Figure was obtained prior to the priority date for the present application. In Figure 1, ESP01 stands for ambroxol, LS stands for alpha-lipoic acid and ESP02 stands for enalapril, which is an ACE inhibitor. As can be seen from this Figure, the combination of ambroxol + α-lipoic acid + elanapril resulted in significant neuro protection in this clinically relevant animal model of neurodegenerative disease. Furthermore, it is apparent from this Figure that the administration of ambroxol (ESP01) alone does **not** result in any significant neuro protection. Therefore, it is clear that the method of the invention, namely administering a combination of ambroxol and an ACE inhibitor, is effective to obtain a synergistic inhibition of neurodegenerative disease in a clinically relevant in vivo model.

Applicants reiterate as set forth in the previous Office Action response and noted above that the presently claimed synergistic effect is also demonstrated in the present specification in Example 3. Moreover, in addition to demonstrating this synergistic effect, Applicants have shown that none of α-lipoic acid, ambroxol or elanapril, when applied alone, were capable of reducing neuronal damage after oxygen glucose deprivation (see page 9, line 21, through line 4, page 10 of the present specification). Thus, contrary to the assertions in the Office Action, the method of the invention is credible and enabled.

Claim rejections under 35 USC 103

The examiner has imposed a rejection of all the claims under 35 USC 103(a) and has asserted that claims 45-86 are unpatentable over Gillissen et al., in further view of Derick et al. and Elena et al., Sian et al. and Kozhevnikova et al.

In response, Applicants reiterate the previously presented arguments that Gillisen et al. do not teach the use of ambroxol for correcting a GSH deficiency, and in no way draw any link between a GSH deficiency and using a combination of ambroxol and any

other agent to obtain a synergistic therapeutic effect on neurodegenerative diseases. In particular, the anti-oxidant activity of ambroxol is described in Gillissen et al. only in the context of the pathology of lung disease, and ambroxol is only generally discussed in Gillissen et al. in respect of the well recognized glutathione redox cycle depicted in Figure 1. Moreover, Gillissen et al. state that ambroxol is capable of reducing oxidant-related cell damage through inhibition of phospholipases, stimulation of the lung surfactant system, inhibition of cytokines, and inhibition of chemotaxis response of neutrophils fMLP (see page 613, top of left column), but do not expressly attribute correction of a GSH deficiency to ambroxol. Therefore, Applicants submit that the assertion that ambroxol is described in this reference as suitable for use in a method of correcting a GSH deficiency is unsupported by the cited reference. Further, the authors of Gillissen et al. fail to provide any teaching, suggestion or motivation even to combine the compositions under their direct investigation, let alone combining them with chemically distinct molecules, such as the presently claimed ACE inhibitors and α-lipoic acid. Further still, this reference does not teach, suggest or motivate alone or in combination with any other reference a method for achieving a synergistic effect on any disease using any combination of enzyme inhibitors, let alone in the manner presently claimed.

With respect to Elena et al., Applicant submits that this reference relates to the anti-oxidative properties of the ACE-inhibitors enalapril and captopril and their effect on the metabolism of compounds with non-protein-bound thiol groups, specifically GSH, but it does not disclose a combination of any ACE-inhibitor and any other substance. Moreover, Elena et al. does not disclose the use of any composition to achieve a synergistic effect on any disease, let alone the use of the present compositions for achieving a synergistic effect. Therefore, this reference does not teach, suggest or motivate the present invention alone or in combination with any other reference.

With respect to Derick et al., this reference also fails to provide any teaching, suggestion or motivation to combine α-liopic with other compounds having similar activity, nor does it disclose any connection between a GSH deficiency and neurodegenerative diseases.

With respect to Sian et al., this reference provides no suggestion, teaching or motivation as to how one would treat Parkinson's disease in any manner, let alone by using the compositions and methods of the present invention.

With respect to Kozheniova et al., this reference discloses the use of ACE inhibitors for treating ischemia, but there is no suggestion, motivation or teaching to combine an ACE inhibitor with any other compound, let alone with ambroxol as disclosed in the present application.

In response to the assertion that the present invention is merely a combination of compounds known to perform the same function individually, Applicants respectfully direct the Examiner's attention to the Declaration of Dr. Frank Striggow and the Figures appended thereto, which demonstrate the unexpected effects of the presently claimed compositions.

In more detail, and as noted above, the combination of ambroxol and an ACE inhibitor provides a synergistic neuroprotective effect in a clinically relevant in vivo model. The same is true for the combination of ambroxol + enalapril + alpha-lipoic acid. However, **no** neuro protective effect is observed after the singular administration of ambroxol. Further, as demonstrated in Figs. 2-4 appended to Dr. Striggow's declaration, the combination of ambroxol + alpha-lipoic acid, or enalapril or alpha-lipoic acid administered individually also have essentially no effect. This is in stark contrast to the conclusion drawn from the cited references in the Office Action, namely, that one skilled in the art would expect each of these compounds alone to exhibit a neuroprotective effect in the method of the present invention, and that one skilled in the art would know to combine them according to the principles of medicinal chemistry.

Thus, Applicants respectfully submit that the present invention, which requires a combination of ambroxol and an ACE inhibitor to have any neuroprotective effect, and moreover demonstrates a synergistic effect of the same, is irrefutably surprising and non-obvious in view of the contrary expectation one skilled in the art would from upon reading the cited references. In this regard, Applicants point out that that MPEP 716.02(a)I indicates that evidence of a greater than expected result may be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism") (citing Merck & Co. Inc. v. Biocraft

Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989).

Applicants further point out that the contention that the present claims are prima facie obvious supported by the statement:

> "Knowing that ambroxile, α-lipoic acid and ACE inhibitors, individually, are useful for Parkinson's disease, neurodegnerative disorders and cerebral ischemia, one of skill in the art would have known to use them individually or combine them in a composition for the diseases." (Office Action, sentence spanning pages 8-9).

Applicants query how the Examiner can adopt the position that it would be obvious to one skilled in the art to use a combination of compounds known to affect GSH to treat neurodegenerative diseases, but also deem the method of the invention "not believable on its face." In this regard, Applicants respectfully submit the Examiner has taken mutually exclusive positions in imposing the present enablement and obviousness rejections.

With respect to the rejection of the claims as claiming the same invention as that of copending application serial nos. 10/478,174 and 10/4790,080, Applicant respectfully requests the Examiner to hold this rejection in abeyance until such time as the present application is otherwise deemed allowable. Applicants also request the Examiner to hold in abeyance the requirement for corrected drawings until such time as the present application is otherwise deemed allowable.

Conclusion

Based on the arguments and amendments presented herein, Applicants believe all the pending claims are now in condition for allowance and respectfully request the Examiner to allow all the claims. Applicants request a two-month extension of time to file this response. A check for the required fee of $450.00 is enclosed. Please charge any additional fees due or credit any overpayment to deposit account number 08-2442.

Respectfully submitted,
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